



130-120-129<sup>9A4</sup>

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE  
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re Application of :  
FISHER et al. : Group Art Unit: 129  
Serial No. 06/853,404 : Examiner: R. Bond  
Filed: April 18, 1986 :  
For: DERIVATIVES OF QUINUCLIDINE

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January 23, 1989

A P P E A L      B R I E F

Honorable Commissioner of  
Patents and Trademarks  
Washington, DC 20231

Sir:

This is an appeal from the Examiner's final Action (Paper No. 11) dated May 10, 1988. A Notice of Appeal was filed November 10, 1988. An Advisory Action was issued November 15, 1988 and a further Advisory Action was issued December 12, 1988.

There are no prior art rejections on appeal. The Appeal is based solely on rejections under 35 U.S.C. 112, first and second paragraphs.

STATUS OF CLAIMS

The claims on appeal define a compound (claims 1-11, 13-17 and 101), a pharmaceutical composition (claims 42-54, 84-86 and 88-90) and a method of use (claims 57-77 and 91-100). Claims 1, 65 and 101 are independent, the remaining claims directly or indirectly depend therefrom.

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Claims 1-100 were filed with the application on April 18, 1986; claims 55, 56 and 87 were cancelled therein by Preliminary Amendment. Claim 12 was cancelled and claim 101 was added by Amendment dated March 21, 1988. Claims 18-41 and 78-83 were cancelled by Amendment dated November 8, 1988.

Claims 1-11, 42-54, 57-71, 84-86 and 88-90 stand rejected on appeal (Final Action dated May 10, 1988, at page 6, paragraph 25). Claims 13-17, 72-77 and 91-101 are objected to "as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form" (Final Action dated May 10, 1988, at page 6, paragraph 26).

A copy of the claims on Appeal are provided in the Appendix.

#### STATUS OF AMENDMENTS

An Amendment after Final Action was filed November 8, 1988 cancelling claims 18-41 and 78-83 without prejudice, and correcting an inadvertent error in the structural formula of claim 1. An Advisory Action dated November 15, 1988 indicated that the Amendment was considered and would be entered upon the filing of an Appeal. A Notice of Appeal was filed November 10, 1988.

A Request for Clarification was filed November 22, 1988 requesting correction of the claim status as set forth in the Advisory Action dated November 15, 1988. The Advisory Action

dated December 12, 1988 modified and corrected the status of the claims.

A proposed Amendment is submitted herewith wherein certain inadvertent, nonsubstantive errors in the claims are corrected.

It is assumed for purposes of appeal that the Amendment is entered since it places the claims in better form for consideration (37 C.F.R. 1.116(a)).

#### SUMMARY OF INVENTION

The present application discloses an invention in (1) spiro(1,3-oxathiolane-5,3')quinuclidine and hydroxymercaptomethyl-quinuclidine compounds (claims 1-11, 13-17 and 101), (2) pharmaceutical compositions containing these compounds (claims 42-54, 84-86 and 88-90), and (3) a method for treating diseases of the central nervous system using these compounds (claims 57-77 and 91-100).

Various neurologic and psychiatric disorders including, but not limited to senile dementia of Alzheimer's type (SDAT), appear to result from a chronic deficiency in the function of acetylcholine as a neurotransmitter (cholinergic function) in the central nervous system. Many cholinergic agonists, primarily muscarinic drugs, have been tested for use in the treatment of SDAT based on their apparent ability to elevate and restore cholinergic activity in the central nervous system. Most of the muscarinic drugs, however, produce significant peripheral adverse

side-effects as well. Thus, there is an urgent need for long-lasting, centrally active cholinomimetic drugs which achieve the beneficial results of the cholinergic agonists, but which do not also produce their undesirable side-effects (page 2, line 3 to page 3, line 23).

Fused-ring quinuclidines have previously been disclosed as psychomotor stimulators (page 1, lines 11-18). Spiro(1,3-dioxolane-4,3')quinuclidines have also been disclosed having one or two alkyl and/or aryl substituents in the 2-position of the dioxolane ring, however, while monomethyl, dimethyl and diphenyl compounds were specifically described, only the monomethyl compound has been disclosed as possessing cholinergic activity (page 1, line 19 to page 2, line 2).

While attempts have been made to improve the therapeutic profile of various pharmacologically active oxathiolane compounds by replacing particular atoms or groups within these compounds, these attempts have generally proven unsuccessful, for the pharmacological activity of the resulting product cannot be predicted with any degree of certainty (page 4, lines 15-24).

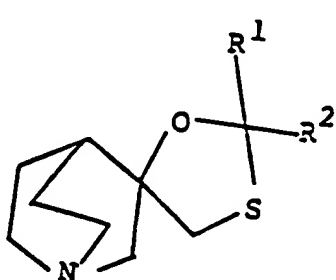
Thus, it was surprising to the present inventors when they found that substitution of the oxygen atom of the dioxolane ring of spiro(dioxolane)quinuclidine with sulfur (an atom having twice the atomic mass of oxygen), at the same time extending the substituents at the 2-position to include diarylmethylo and

alkyl substituted by aryl, produced pharmacologically improved, cholinergically active compounds.

These compounds are advantageous over previously disclosed compounds, for in addition to possessing cholinergic activity they possess less pronounced side-effects than those previously achieved, namely, sialogenic and tremorigenic activity (page 4, line 25 to page 5, line 15).

No prior art has been cited against the claims on appeal.

The claims on appeal accordingly first define compounds of the formula (I)



Formula (I)

and geometrical isomers, enantiomers, diastereoisomers, racemates and/or acid addition salts thereof, wherein R<sup>1</sup> is selected from the group consisting of hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethylol and lower alkyl which is substituted by one or two phenyl groups and R<sup>2</sup> is selected from the group consisting of lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethylol and lower alkyl which is substituted by one or two phenyl groups (e.g. claims 1-11 and 13-17). The preferred best mode compound 3-hydroxy-3-mercaptomethyl quinuclidine (claim 101) is defined as well.

The claims further define pharmaceutical compositions comprising a compound of formula (I), above, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent (e.g. claims 42-54, 84-86 and 88-90).

Other claims on appeal define methods for treating diseases of the central nervous system in mammals, comprising administering to the mammal a compound of formula (I), above, or a pharmaceutically compatible acid addition salt thereof (e.g. claims 57-77 and 91-100).

#### ISSUES

1. Are compound claims 1-11, composition claims 42-54, 84-86 and 88-90, and method claims 57-71 properly rejected as unpatentable under 35 U.S.C. 112, first and second paragraphs, as nonenabling and/or as failing to particularly point out and distinctly claim the subject matter of the invention?

2. Are compound claims 13-17 and 101, and method claims 72-77 and 91-100 properly rejected as unpatentable as being dependent upon rejected base claims?

3. Are composition claims 42-54, 84-86 and 88-90 properly rejected as being too vague and indefinite in the recitation of "pharmaceutical," "to constitute a utility within the meaning of 35 U.S.C. 101" (Paper No. 11, page 3, paragraph 8)?

### GROUPING OF CLAIMS

1. All arguments pertaining to the particularity and distinctness of the claim language apply with equal force to compound claims 1-11, composition claims 42-54, 84-86 and 88-90, and method claims 57-71.
2. Separate arguments are provided with respect to the rejection of claims 13-17, 72-77 and 91-100, and claim 101 as being dependent upon a rejected base claim.
3. All arguments pertaining to the composition claims and the use therein of the term "pharmaceutical" apply only to claims 42-54, 84-86 and 88-90.

### ARGUMENT

1. The Examiner asserted that the present claims were indefinite in regard to the "R" substituents on the structural formula set forth in claim 1. This is a mere clerical error in failing to set forth the intended "R<sup>1</sup>" and "R<sup>2</sup>" symbology.

Appellants have since amended the formula (I) of claim 1 so as to define the R substituents individually as R<sup>1</sup> and R<sup>2</sup>. Support for the amended language appears at pages 5-6 of the specification.

Additionally, a proposed amendment further correcting the text of amended claim 1 wherein the superscript numeral 2 of

the R substituent (line 9) was inadvertently omitted from the claim language has been submitted. It is appellants belief that the claims, as now amended, do particularly and distinctly define the invention of the present application. Thus, appellants submit that claims 1-11, 42-54, 57-71, 84-86 and 88-90 are in condition for allowance.

2. Appellants further submit that claims 13-17, 72-77 and 91-100, which were objected to as being dependent on rejected claims are now similarly in condition for allowance as depending from allowable claims.

Claim 101 stands rejected as being dependent upon a rejected base claim. Appellants submit that this rejection is improper in view of the fact that claim 101 is an independent claim. No other basis for rejection of this claim has been recited. Claim 101 is therefore in condition for allowance.

3. Use of the term "pharmaceutical" in claims 42-54, 84-86 and 88-90 is objected to and the claims rejected, as being "too vague and indefinite to constitute a utility within the meaning of 35 USC 101." The Examiner alleged that to overcome this rejection a definite use had to be recited in the composition claims, such as those uses recited in the method claims. "Both types of claims require the recitation of a definite use or uses" (Paper No. 11, page 3, paragraph 9). In support of this allegation the Examiner cited In re Kirk and Petrow, 153 USPQ 48 (CCPA 1967) and In re Joly and Warrant, 153 USPQ 45 (CCPA 1967).



Appellants respectfully submit that the utility of a claimed composition need not be recited in the claims of a patent application. A disclosure of utility is required to be set forth in the specification to establish patentable subject matter under 35 U.S.C. 101. However, claims to a composition of matter, unlike a method of use, do not require recitation of a specified utility therein.

The specification of the instant application discloses definite and credible utilities for the claimed invention on pages 20, 21, 62-79 which include among others, a method for treating diseases of the central nervous system, and use of the disclosed compounds for treating these diseases.

It is not questioned that the composition claims adequately define the active compound and additional ingredients of the composition. Therefore, in view of the admitted usefulness of the compositions of the present invention (based on the disclosure in the specification) the composition claims are clearly adequately defined under 35 U.S.C. 112.

With regard to the cited cases, appellants have reviewed these decisions and nowhere find therein any support for the Examiner's allegations. These cases merely provide that an essential element of patentable subject matter is that a utility is disclosed for the claimed compositions in the specification of the application. These cases were concerned with the nature of the stated utilities, and so not stand for the proposition that

the disclosed utilities must also be recited in the composition claims.

In view of the above arguments, appellants respectfully submit that claims 1-11, 13-17, 42-54, 57-71, 84-86 and 88-101 are patentable and should be passed to issue.

Respectfully submitted,

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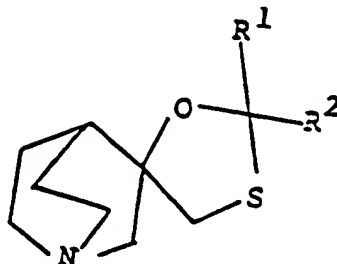
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## A P P E N D I X

### Claims

1. A compound of the formula (I)



and geometrical isomers, enantiomers, diastereoisomers, racemates and/or acid addition salts thereof, wherein R<sup>1</sup> is selected from the group consisting of hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethanol and lower alkyl which is substituted by one or two phenyl groups and R<sup>2</sup> is selected from the group consisting of lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethanol and lower alkyl which is substituted by one or two phenyl groups.

2. A compound according to claim 1, wherein R<sup>1</sup> is hydrogen, and R<sup>2</sup> is selected from the group consisting of lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethanol and lower alkyl which is substituted by one or two phenyl groups.

3. A compound according to claim 1, wherein R<sup>1</sup> is selected from the group consisting of lower alkyl, cyclopentyl and cyclohexyl, and R<sup>2</sup> is selected from the group consisting of

lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethanol and lower alkyl which is substituted by one or two phenyl groups.

4. A compound according to claim 1, wherein  $R^1$  is phenyl, and  $R^2$  is selected from the group consisting of phenyl, diphenylmethanol and lower alkyl which is substituted by one or two phenyl groups.

5. A compound according to claim 2, wherein  $R^1$  is hydrogen and  $R^2$  is methyl.

6. A compound according to claim 2, wherein  $R^1$  is hydrogen and  $R^2$  is phenyl.

7. A compound according to claim 2, wherein  $R^1$  is hydrogen and  $R^2$  is diphenylmethyl.

8. A compound according to claim 2, where  $R^1$  is hydrogen and  $R^2$  is selected from the group consisting of ethyl, propyl and diphenylmethanol.

9. A compound according to claim 3, wherein  $R^1$  is methyl and  $R^2$  is phenyl.

10. A compound according to claim 3, wherein  $R^2$  is phenyl and  $R^1$  is selected from the group consisting of ethyl and cyclohexyl.

11. A compound according to claim 4, wherein R<sup>1</sup> and R<sup>2</sup> are each phenyl.

13. The geometrical isomer of the compound according to claim 5, the hydrochloric acid salt of which has the relatively lower melting-point (the cis-isomer).

14. The geometrical isomer of the compound according to claim 5, the hydrochloric acid salt of which has the relatively higher melting-point (the trans-isomer).

15. The hydrochloric acid salt of the compound according to claim 5.

16. The relatively lower melting-point geometrical isomer (the cis-isomer) of the compound according to claim 15.

17. The relatively higher melting-point geometrical isomer (the trans-isomer) of the compound according to claim 15.

42. A pharmaceutical composition comprising a compound of formula (I) according to claim 1, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent.

43. A pharmaceutical composition according to claim 42, which is in a form suitable for oral, rectal or parenteral administration, or for administration by insufflation.

44. A pharmaceutical composition according to claim 42, which is in a form suitable for transdermal administration.

45. A pharmaceutical composition according to claim 42, which is in unit dosage form.

46. A pharmaceutical composition for transdermal administration, comprising a compound of formula (I) according to claim 1, or a pharmaceutically compatible acid addition salt thereof, and a low molecular weight fatty acid.

47. A pharmaceutical composition according to claim 42, wherein the compound of formula (I) is that in which  $R^1$  is phenyl, and  $R^2$  is selected from the group consisting of ethyl, cyclohexyl and phenyl.

48. A pharmaceutical composition according to claim 42, wherein the compound of formula (I) is that in which  $R^1$  is hydrogen, and  $R_2$  is selected from the group consisting of methyl and ethyl.

49. A pharmaceutical composition according to claim 42, wherein the compound of formula (I) is that defined in claim 13.

50. A pharmaceutical composition according to claim 49, further comprising one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

51. A pharmaceutical composition according to claim 42, wherein the compound of formula (I) is that in which  $R^2$  is selected from the group consisting of lower alkyl containing at least three carbon atoms, cyclopentyl, cyclohexyl, phenyl, diphenylmethylol and lower alkyl substituted by one or two phenyl groups, and  $R^1$  is selected from the group consisting of hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethylol and lower alkyl substituted by one or two phenyl groups.

52. A pharmaceutical composition according to claim 51, wherein the compound of formula (I) is that in which  $R^1$  is methyl and  $R^2$  is phenyl.

53. A pharmaceutical composition according to claim 51, wherein the compound of formula (I) is that in which  $R^1$  is hydrogen and  $R^2$  is diphenylmethyl.

54. A pharmaceutical composition according to claim 51, wherein the compound of formula (I) is that in which  $R^1$  is

hydrogen, and  $R^2$  is selected from the group consisting of propyl, phenyl, and diphenylmethanol.

57. A method for treating diseases of the central nervous system in mammals, comprising administering to the mammal a compound of formula (I) according to claim 1 or a pharmaceutically compatible acid addition salt thereof.

58. A method for treating diseases of the central nervous system in mammals, comprising administering to the mammal a pharmaceutical composition according to claim 42.

59. A method for treating diseases of the central nervous system in mammals, comprising transdermal administration to the mammal of a compound of formula (I) according to claim 1 or a pharmaceutically compatible acid addition salt thereof.

60. A method for treating diseases due to a deficiency in the central cholinergic system in mammals, comprising administering to the mammal a compound according to claim 2, wherein  $R^1$  is hydrogen and  $R^2$  is methyl, or geometrical isomers, enantiomers, racemates or acid addition salts thereof.

61. A method for treating diseases due to a deficiency in the central cholinergic system in mammals, comprising administering to the mammal a pharmaceutical composition containing a compound according to claim 2, wherein  $R^1$  is



hydrogen and  $R^2$  is methyl, or geometrical isomers, enantiomers, racemates or acid addition salts thereof, together with an inert carrier or diluent.

62. A method for treating diseases due to a deficiency in the central cholinergic system in mammals, comprising transdermal administration to the mammal of a compound according to claim 2, wherein  $R^1$  is hydrogen and  $R^2$  is methyl, or geometrical isomers, enantiomers, racemates or acid addition salts thereof.

63. A method for treating diseases due to cholinergic hyperfunction in mammals, comprising administering to the mammal a pharmaceutical composition containing a compound of formula (I) according to claim 1 or a pharmaceutically compatible acid addition salt thereof, wherein  $R^2$  is selected from the group consisting of lower alkyl containing at least three carbon atoms, cyclopentyl, cyclohexyl, phenyl, diphenylmethylol and lower alkyl substituted by one or two phenyl groups, and  $R^1$  is selected from the group consisting of hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethylol and alkyl substituted by one or two phenyl groups.

64. A method for treating diseases due to cholinergic hyperfunction in mammals, comprising administering to the mammal a pharmaceutical composition containing a compound of formula (I) according to claim 1 or a pharmaceutically compatible acid addition salt thereof, wherein  $R^2$  is selected from the group

consisting of lower alkyl containing at least three carbon atoms, cyclopentyl, cyclohexyl, phenyl, diphenylmethanol and lower alkyl substituted by one or two phenyl groups, and  $R^1$  is selected from the group consisting of hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethanol and alkyl substituted by one or two phenyl groups, together with an inert carrier or diluent.

65. A method for treating diseases due to cholinergic hyperfunction in mammals, comprising transdermal administration to the mammal of a compound of formula (I) or a pharmaceutically compatible acid addition salt thereof, wherein  $R^2$  is selected from the group consisting of lower alkyl containing at least three carbon atoms, cyclopentyl, cyclohexyl, phenyl, diphenylmethanol and lower alkyl substituted by one or two phenyl groups, and  $R^1$  is selected from the group consisting of hydrogen, lower alkyl, cyclopentyl, cyclohexyl, phenyl, diphenylmethanol and lower alkyl substituted by one or two phenyl groups.

66. A method of treating diseases due to cholinergic hyperfunction in mammals, comprising administering to the mammal a compound according to claim 7, or a pharmaceutically compatible acid addition salt thereof.

67. A method for treating diseases due to cholinergic hyperfunction in mammals, comprising administering to the mammal a pharmaceutical composition containing a compound according to

claim 7, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent.

68. A method for treating diseases due to a deficiency in the central cholinergic system in mammals, comprising transdermal administration to the mammal of a compound according to claim 7, or a pharmaceutically compatible acid addition salt thereof.

69. A method for treating diseases due to cholinergic hyperfunction in mammals, comprising administering to the mammal a compound according to claim 9, or a pharmaceutically compatible acid addition salt thereof.

70. A method for treating diseases due to cholinergic hyperfunction in mammals, comprising administering to the mammal a pharmaceutical composition containing a compound according to claim 9, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent.

71. A method for treating diseases due to cholinergic hyperfunction in mammals, comprising transdermal administration to the mammal of a compound according to claim 9, or a pharmaceutically compatible acid addition salt thereof.

72. A method for treating senile dementia of Alzheimer's type, comprising administering to a patient a compound according

to claim 13, or a pharmaceutically compatible acid addition salt thereof.

73. A method for treating senile dementia of Alzheimer's type, comprising administering to a patient a pharmaceutical composition containing a compound according to claim 13, or a pharmaceutically compatible acid addition salt thereof, together with an inert carrier or diluent.

74. A method for treating senile dementia of Alzheimer's type, comprising transdermal administration to a patient of a compound according to claim 13, or a pharmaceutically compatible acid addition salt thereof.

75. A method according to claim 72 wherein there is coadministered with said compound, one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

76. A method according to claim 73 wherein there is coadministered with said compound, one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

77. A method according to claim 74 wherein there is coadministered with said compound, one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, 4-aminopyridine and 3,4-diaminopyridine.

84. A pharmaceutical composition in unit dosage form comprising a compound of formula (I) according to claim 1, or a pharmaceutically compatible acid addition salt thereof, in an amount ranging from about 0.5 to about 500 mg., together with an inert carrier or diluent.

85. A pharmaceutical composition according to claim 84 comprising the said compound, or a pharmaceutically compatible acid addition salt thereof, in an amount in the range of about 5 to about 100 mg.

86. A pharmaceutical composition according to claim 85 comprising the said compound, or a pharmaceutically compatible acid addition salt thereof, in an amount in the range of about 10 to about 50 mg.

88. A pharmaceutical composition according to claim 84, further comprising one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

89. A pharmaceutical composition according to claim 84, wherein the composition is adapted for oral administration.

90. A pharmaceutical composition according to claim 84, wherein the composition is adapted for parenteral administration.

91. A method for treating senile dementia of Alzheimer's type, comprising orally administering to a patient a compound according to claim 13, or a pharmaceutically compatible acid addition salt thereof, in an amount ranging from about 0.1 to about 60 mg./kg. body weight.

92. A method according to claim 91 wherein said amount ranges from about 0.5 to about 10 mg./kg. body weight.

93. A method according to claim 92 wherein said amount ranges from about 1 to about 5 mg./kg. body weight.

94. A method according to claim 91, wherein there is coadministered with the said compound, one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

95. A method according to claim 91, wherein administration is by means of a pharmaceutical composition in unit dosage form comprising the said compound in an amount ranging from about 0.5 to about 500 mg., together with an inert carrier or diluent.

96. A method for treating senile dementia of Alzheimer's type, comprising parenterally administering to a patient a compound according to claim 13, or a pharmaceutically compatible acid addition salt thereof, in an amount ranging from about 0.01 to about 40 mg./kg. body weight.

97. A method according to claim 96 wherein said amount ranges from about 0.05 to about 5 mg./kg. body weight.

98. A method according to claim 97 wherein said amount ranges from about 0.1 to about 2 mg./kg. body weight.

99. A method according claim 96, wherein there is coadministered with the said compound, one or more compounds selected from the group consisting of physostigmine, tetrahydroaminoacridine, choline, lecithin, piracetam, aniracetam, pramiracetam, oxiracetam, 4-aminopyridine, 3,4-diaminopyridine and somatostatin.

100. A method according to claim 96, wherein administration is by means of a pharmaceutical composition in

unit dosage form comprising the said compound in an amount ranging from about 0.5 to about 500 mg., together with an inert carrier or diluent.

101. The compound 3-hydroxy-3-mercaptomethyl quinuclidine.